BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellant(s): Annaliesa S. Anderson, *et al.*

Application Number: 10/564,458

Filing Date: January 12, 2006

Title of the Invention: POLYPEPTIDES FOR INDUCING A PROTECTIVE IMMUNE RESPONSE AGAINST STAPHYLOCOCCUS AUREUS

Examiner: Devi, Sarvamangala

Art Unit: 1645

APPEAL BRIEF

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REAL PARTY IN INTEREST

The real party in interest is Merck Sharp & Dohme Corp., the current assignee, which is a subsidiary of Merck & Co., Inc.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences. A divisional application, U.S. Serial No. 12/771,345, was filed April 30, 2010.

STATUS OF CLAIMS

The status of the claims is as follows: claims 5, 6 and 36 are objected to; claims 1, 4, 7-9, 33-35 and 38-54 are rejected; and claims 2, 3, 10-32 and 37 are canceled. The rejection of claims 1, 4, 7-9, 33-35 and 38-54 is being appealed; and the objection to claims 5, 6 and 36 is being appealed.

STATUS OF AMENDMENTS

An amendment after final was filed February 24, 2010. The advisory action mailed March 25, 2010 indicated for the purposes of appeal the amendment would be entered.

SUMMARY OF CLAIMED SUBJECT MATTER

The pending claims provide for immunogens able to induce a protective immune response against *S. aureus*. The present application illustrates the ability of a full-length *S. aureus* protein designated "ORF0657n", and ORF0657n fragments containing "ORF0657nH" and "ORF0657nI" regions, to provide protective immunity in an animal model against different strains of *S. aureus*. (See, for example, the present application Figure 1; Example 3 on page 26, line 17 to page 27, line 2; Example 6 on page 29, lines 10-21; and Example 16 on page 50, line 30 to page 51, line 22.)

ORF0657n is a protein located on the *S. aureus* cell wall. (The present application at page 19, lines 9-18.) The polypeptide immunogens used to induce the immune response illustrated in the application were based on a different ORF0657n sequence than that present in the *S. aureus* challenge strain used in the protection experiments. The full-length ORF0657n sequences present in the different *S. aureus* challenge strains and the full-length *S. aureus* sequence upon which the polypeptide immunogen had a sequence identity of at least 94%. (See, for example, the present application Example 3 on page 26, line 17 to page 27, line 2, Figures 3A-3B and description of the figures on page 5, lines 16-23; Example 6 on page 29, lines 10-21, Figures 4A-4H, and description of the figures on page 5, lines 23-31; and Table 3 on pages 28 and 29.)

Independent claim 1 is directed to a purified polypeptide immunogen consisting of either (a) an amino acid sequence at least 94% identical to SEQ ID NO: 3, or (b) a fragment of said amino acid sequence, where said fragment comprises an amino acid sequence at least 94% identical to SEQ ID NO: 1. The polypeptide immunogen provides protective immunity against *S. aureus*. A purified polypeptide is defined in the application on page 14, lines 18-30.

SEQ ID NOs: 1 and 3 provide sequences corresponding to an ORF0657nI region and an ORF0657nH region, respectively, to which an amino terminus methionine is added. (The present application at page 8, Table 1 description.)

Support for the sequence identity description is provided in the application on page 14, lines 6-10 (referring to sequence identity of at least 94% to SEQ ID NO: 3 or a fragment thereof comprising an amino acid sequence structurally related to SEQ ID NO: 1), and page 12, lines 33-35, describing an embodiment where the SEQ ID NO: 1 related polypeptide region is at least 94% identical to SEQ ID NO: 1.

Independent claim 5 is directed to a polypeptide immunogen consisting of the amino acid sequence of SEQ ID NO: 1, 3, 7, 17, 20, or 42, each with up to 20 additional amino acids. The up to 20 additional amino acids can be located at the carboxyl or the amino terminus.

SEQ ID NO: 1, 3, 7, 17, 20, or 42 are described in the application on Table 1, pages 8 and 9, and the Sequence Listing. Original claim 5 referred to these sequences and used the language "consists essentially of". "Consists essentially of" is defined in the application on page 13, lines 14-17, and provides support for the up to 20 amino acid additions.

Independent claim 7 is directed to an immunogen consisting of an amino acid sequence at least 90% identical to SEQ ID NO: 1 and one or more additional regions or moieties covalently joined to the sequence at the carboxyl terminus or the amino terminus. Each of the additional regions or moieties is independently selected from a region or moiety having at least one of the following properties: enhances the immune response, facilitates purification, or facilitates polypeptide stability. Support for claim 7 is provided in the application, for example, on page 2, line 30 to page 3, line 2. Reference to additional regions or moieties is defined in the application on page 3, lines 3-6.

Independent claim 8 is directed to a composition able to induce a protective immune response against *S. aureus* in a patient. The composition comprises an immunologically effective amount of a purified polypeptide immunogen that provides protective immunity against *S. aureus* and a pharmaceutically acceptable carrier. The polypeptide immunogen consists of either (a) an amino acid sequence at least 94% identical to SEQ ID NO: 3, or (b) a fragment of said amino acid sequence at least 94% identical to SEQ ID NO: 3, where said fragment comprises an amino acid sequence at least 94% identical to SEQ ID NO: 1.

The present application provides support for a composition able to provide a protective immune response on, for example, page 3, lines 7-10. Purified polypeptide is defined in the application on page 14, lines 18-30. Support for the sequence identity description is provided in the application on page 14, lines 6-10 (referring to sequence identity of at least 94% to SEQ ID NO: 3 or a fragment thereof comprising an amino acid sequence structurally related to SEQ ID NO: 1), and page 12, lines 33-35, describing an embodiment where the SEQ ID NO: 1 related polypeptide region is at least 94 % identical to SEQ ID NO: 1.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Claims 1, 4, 7-9, 33-35, 38-44 and 49-51 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing inadequate written description

II. Claim 8 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite

III. Claim 7 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite

IV. Claims 9 and 38-54 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite

V. Claims 5 and 6 stand objected to as covering a non-elected and non-searched species

VI. Claim 36 stands objected to based on its dependency from claim 6

ARGUMENT

I. The Present Application Reasonably Conveys to Those Skilled in the Art that the Inventors had Possession of the Subject Matter of Claims 1, 4, 7-9, 33-35, 38-44 and 49-51

The written description rejection to claims 1, 4, 7-9, 33-35, 38-44 and 49-51 is directed to the provided descriptions of sequence identity or amino acid alterations. The rejected claims include descriptions providing for at least 90% identity to SEQ ID NO: 1, at least 94% identity to SEQ ID NO: 1, or up to 5, 10, or 25 amino acid alterations from SEQ ID NO: 1.

The present application clearly reasonably conveys to those skilled in the art the inventors had possession of the claimed subject matter as of the filing date by providing representative species of polypeptides within the claimed genus. Representative species of polypeptides are illustrated by the use of SEQ ID NO: 1, and longer-length polypeptides containing a SEQ ID NO 1 region, to provide protection against heterologous challenge strains of *S. aureus*. The "challenge strain" is the *S. aureus* used to infect a host. The heterologous challenge experiments described in the application involved a *S. aureus* challenge strain having a different ORF0657n region than the corresponding region present in the protective immunogen.

The ability of a polypeptide to provide protection against a heterologous strain of *S. aureus* demonstrates that alterations can be made to SEQ ID NO: 1 where protection is maintained and provides a strong expectation that the corresponding region from the challenge strain could also provide protection. For example, the ORF0657nI region from the challenge strain could be used to provide homologous protection, where the protective polypeptide has the same ORF0657nI region as the challenge strain. Examples of corresponding sequences from other strains of *S. aureus* are provided in the application. (The present application Figures 2A to 2E.)

The data provided with different polypeptides illustrate that the claimed genus is reasonably related to the provided structural descriptions, provides evidence that other species described in the application are protective, and supports further variations of the protective polypeptides beyond those actually tested. Thus, the data provided in the application in addition to supporting representative species also supports a combination of structure and function commensurate with the scope of the claims.

The test for written description sufficiency is whether the disclosure of the application relied upon reasonable conveys to those skilled in the art the inventor possessed the claimed subject matter as of the filing date. *Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.,* 598 F.3d 1336, 1351, 94 USPQ2d 1161, 1172 (Fed. Cir. Mar. 22, 2010) (citing *Vas-Cath Inc. v. Makurkar* 935 F.2d. 1555, 1562-1563, [19 USPQ2d 1111, 1117] (Fed. Cir. 1991).

Written description of a genus requires a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus. *University of California v. Eli Lilly & Co.,* 119 F.3d 1559, 1568-1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The written description requirement can be satisfied by:

> Show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.,* complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics.

Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 964, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002), citing to and discussing Patent Office Written Description Guidelines provided in 66 Fed. Reg. 1099, 1106 (January 5, 2001).

For the written description rejection, the claims are argued separately in different groups based on the sequence identity or number of alterations, as follows: (A) claims 1, 8, 9, and 38; (B) claim 4; (C) claims 33, 39, 40, and 49; (D) claims 34, 41, 42, and 50; (E) claims 35, 43, 44, and 51; and (F) claim 7.

A. The Data and Guidance in the Application Provides Written Description Support for claims 1, 8, 9, and 38

Claims 1, 8, 9, and 38 include a description of a protective polypeptide immunogen with an amino acid sequence at least 94% identical to SEQ ID NO: 3 or a fragment of said amino acid sequence comprising a sequence at least 94% identical to SEQ ID NO: 1. Claim 1 is directed to the polypeptide immunogen. Claims 8 and 9 are directed to a composition containing the immunogen and a pharmaceutically acceptable carrier, where the composition can provide protective immunity in a patient. Claim 38 depends from claim 8, and further describes the polypeptide immunogen as substantially purified and the patient as a human.

The present application reasonable conveys to one skilled in the art possession of the polypeptide immunogen described in claims 1, 8, 9, and 38, by providing examples of different polypeptides either shown to provide protection or, based on the present application, expected to provide protection, and providing sequence information on different *S. aureus* strains. The present application in Example 3 provides protection data using different polypeptide immunogens containing an ORF0657nI region from SEQ ID NO: 1 against the heterologous *S. aureus* strain Becker. (The present application at page 26, line 18 to page 27, line 2, Figure 3A-3C, and description of the figures on page 5, lines 16-33.) The present application in Example 6 illustrates the ability of a full-length construct containing an ORF0657nI region from SEQ ID NO: 1 to provide protection against different heterologous clinical isolates. (The present application at page 29, line 10 to page 29, line 21, Figures 4A-4H and the description of the figures on page 5, lines 23-32.) The present application in Example 16 illustrates the use of different polypeptides to provide protection. (The present application at page 50, line 30 to page 51, line 21, and Figure 10.)

The regions of ORF0657 used in different protective immunogens are illustrated by Figure 1 of the present application. Figure 1 illustrates the full-length COL *S. aureus* ORF0657n and the location of different regions including ORF0657nI and ORF0657nH. SEQ ID NO: 1 provides the sequence for an ORF0657nI region for *S. aureus* COL, and SEQ ID NO: 3 provides the sequence for ORF0657nH region for *S. aureus* COL. Both SEQ ID NOs: 1 and 3 have a methionine added to the amino terminus. (The present application at page 8, Table 1.)

The data illustrated in Examples 3, 6 and 16 identifies SEQ ID NO: 1 as sufficient to induce a protective immune response, illustrates the ability of SEQ ID NO: 1 to provide protective immunity against *S aureus* strain Becker, and illustrates the ability of longer-length polypeptides containing SEQ ID NO: 1 to provide protection against different heterologous clinical isolates of *S. aureus*. Strain Becker ORF0657n has a sequence identity of 95% to the COL ORF0657n sequence. (The present application at page 29, Table 3.). The different clinical isolate *S. aureus* strains have an ORF0657n differing from COL ORF0657n by up to 94%. (See the description of Figures 4A-4H on page 5, lines 23-32 and Table 3 on page 28 to 29.)

The ability of a particular polypeptide to induce an immune response against a heterologous strain provides important information concerning both the range of *S. aureus* that can be targeted by a particular polypeptide and variations in polypeptide structure that can made

and still retain the ability to induce protective immunity. A polypeptide inducing protective immunity generates an immune response against a target present on the challenge strain.

The ability to induce an immune response against heterologous strains indicates that regions involved in the protective immune response are present in both the employed polypeptide immunogen and the challenge strain. The corresponding challenge strain sequence would be expected to also induce an immune response, for example, when used in a homologous challenge. The expectation is based on a homologous challenge involving the use of a polypeptide immunogen having the same region as the challenge strain, where in a heterologous challenge the sequence used to induce the immune response is different from that actually present.

The rejection is improperly based on the possibility that some unidentified alteration could negatively impact the ability of a protective polypeptide to continue to provide protection. The rejection fails to provide support concerning the likelihood that alterations could occur in an essential region within the described genus, such that a significant number of polypeptide immunogens within the described genus would not be protective. The rejection also fails to take into account the importance of data in the application concerning protection in heterologous strains of *S. aureus,* guidance provided concerning the OF0657nI region, and guidance concerning different ORF0657nI sequences. The Patent Office bears the initial burden of presenting a *prima facie* case of unpatentability. *In re Oetiker* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

1. Sequences Used to Generate Protection Data and Target Sequence Information

The protection data provided in Examples 3, 6 and 16 was generated employing different constructs such as SEQ ID NO: 3, SEQ ID NO: 4 containing a carboxyl His-Tag, SEQ ID NO: 5 containing a carboxyl His-Tag, and SEQ ID NO: 28 (corresponding to a full-length sequence with a His-Tag). SEQ ID NOs: 1 and 5 provide a protective region corresponding to an ORF0657nI region. (The present application at page 8, Table 1 description.) SEQ ID NOs: 3 and 4 provide a protective region corresponding to an ORF0657nH region. (The present application at page 8, Table 1 description.)

Exhibit A (provided in the Evidence Appendix), is a sequence comparison of SEQ ID NOs: 1, 3, 4, 5 and 28. The leader sequence and the sortase cleavage site are noted in the sequence comparison. The sequence comparison also highlights amino acids at a couple of variable amino acids present in SEQ ID NOs: 1, 3, 4, 5 and 28. Figures 2A-2E, which were present in the filed application, provides a sequence comparison of different ORF0657n sequences across the ORF0657nH region and includes SEQ ID NOs: 1, 3, 4, and 5.

The Exhibit A sequence comparison provides a useful illustration of the SEQ ID NO: 28 region expected to be involved in producing protective immunity. Both the leader sequence and LPXTG are cleavage points during cellular processing. (See, for example, the present application at page 19, lines 9-18.) Cleavage at the LPXTG motif is indicated in Exhibit A by reference to the "Sortase Cleavage Site". The SEQ ID NO: 28 region expected to be present in the cell wall corresponds approximately to the ORF0657nH region of SEQ ID NO: 3. The expected SEQ ID NO: 28 cell wall region has four additional carboxyl amino acids than SEQ ID NO: 3.

2. Example 3: Protective Immunity in *S. aureus* Strain Becker

Example 3 illustrates the ability of polypeptides of SEQ ID NOs: 4, 5 and 28 to provide protection against *S. aureus* strain Becker. The full-length ORF0657n *S. aureus* strain Becker contains 95% sequence identity to the full-length ORF0657n COL sequence (SEQ ID NO: 2). (See the present application at page 29, Table 3.) SEQ ID NOs: 1, 3, 4, 5 and 28 are based on the COL sequence. (See, for example, the present application at page 8, lines 7-11 and lines 16-18.)

The ability of SEQ ID NO: 5 to provide protective immunity against the heterologous *S. aureus* strain Becker demonstrates the ORF0657nI region, such as that provided by SEQ ID NO: 1, is sufficient to generate a protective immune response. SEQ ID NOs: 4 and 28 are longer length polypeptides containing the SEQ ID NO: 1 ORF0657nI region.

The polypeptide providing an ORF0657nI region (SEQ ID NO: 5) generated at least an equal level of protection to the polypeptide providing the ORF0657nH region (SEQ ID NO: 4). The data provides evidence that ORF0657nH does not contain a critical region beyond that provided by the ORF0657nI region. (See the present application Figure 3B and 3C.)

The protection data also illustrates that SEQ ID NO: 1 is representative of the scope of the claims; and that alterations to the sequences used in the application could be made, where the

resulting immunogens would be protective. For example, the skilled artisan could expect the naturally occurring sequence present in the *S. aureus* Becker strain to provide protective immunity against at least strain Becker. Such an expectation is based on, for example, a polypeptide providing an ORF0657nI or ORF0657nH region based on strain Becker having a greater degree of homology to strain Becker ORF0657n than SEQ ID NOs: 4 or 5.

Based on random chance, one of ordinary skill in art would expect amino acid differences between *S. aureus* strain Becker and COL to be located in different regions including the ORF0657nI. Figures 2A-2E confirm such expectation by providing evidence that differences among different ORF0657n present in different strains occur in different locations including the OFR0657nI region.

A sequence comparison between the strain Becker ORF0657n, SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5 is attached hereto as Exhibit B (provided in the Evidence Appendix). The sequence comparison confirms the evidence provided in the application, and what would be expected by one skilled in the art, concerning the presence of different alterations between COL and Becker being located in different regions.

3. Example 6: Protection Data Against Different Clinical Isolates

The present application illustrates the ability of the polypeptide of SEQ ID NO: 28 to provide protection against different clinical strains of *S. aureus* strains. (The present application at Example 6, page 29, Figures 4A-4H, and description of the figures provided on page 5, lines 23-31.) The ability of a full-length ORF0657n to provide protective immunity against different clinical isolates further supports SEQ ID NO: 1 being representative of the claimed genus; provides support for additional representative species described in the application being protective; and confirms the expectation that alterations can be made to a SEQ ID NO: 1, where the resulting polypeptide retains its protective ability.

The relevance of the data generated with the full-length ORF0657n for the ORF0657nI and ORF0657nH regions can be illustrated by reference to Figures 2A-2E of the present application and Exhibit A. The ORF0657nI region of SEQ ID NO: 1 illustrated in Figures 2A-2E starts at amino acid 3 and runs to the end of SEQ ID NO: 1. The ORF0657nH region of SEQ ID NO: 3 illustrated in Figures 2A-2E goes from amino acid 3 to the end of SEQ ID NO: 3.

Figures 2A-2E illustrates examples of differences between SEQ ID NOs: 1 and 3, and different naturally occurring sequences.

Exhibit A illustrates the processing sites of ORF0657n that produce a region expected to be present in the *S. aureus* wall. Due to processing of the leader sequence and the sortase cleavage site, a region approximately corresponding to the ORF0657nH is expected to be present.

The portion of SEQ ID NO: 28 potentially involved in providing protective immunity is that portion generating an immune response against a polypeptide present on the cell wall. For SEQ ID NO: 28, the relevant region corresponds to the SEQ ID NO: 3 ORF0657nH region plus an additional four amino acids, which provides for a sequence identity of 568 amino acids out of 572 amino acids or over 99%.

The ORF0657nI region of SEQ ID NO: 1 has a significant overlap with the portion of SEQ ID NO: 28 remaining after cellular processing. The overlap contains an exact match of 445 amino acids out of 572. The overlap runs across about 78% of the relevant portion of SEQ ID NO: 28. Example 3 of the present application illustrates that the ORF0657nI region is sufficient to provide protective immunity.

Figures 4A-4H of the present application illustrate the ability of SEQ ID NO: 28 to provide protection against different heterologous clinical isolates designated CL-10, CL-13, CL-30, CL-18 and CL 21. With respect to the Figures 2A-2E sequence alignment: CL-10 corresponds to ID11, CL-13 corresponds to ID19, CL-18 corresponds to ID-18, CL-21 corresponds to ID-22, and CL30 corresponds to ID24.

CL-10, CL-13, CL-30, CL-18 and CL 21 are diverse *S. aureus* strains with different degrees of sequence identity to SEQ ID NO: 2. (The present application at pages 28 and 29, Table 3.) CL-10 has 97% sequence identity to SEQ ID NO: 2, CL-13 has 99% sequence identity to SEQ ID NO: 2, CL-21 is a methicillin resistant strain with 94% sequence identity to SEQ ID NO: 2, and CL-30 has a 96% sequence identity to SEQ ID NO: 2.

Based on the data with different clinical isolates, additional species described in the application that are within the genus are expected to provide protective immunity. Examples of ORF0657nI polypeptides are provided by the present application on page 13, lines 3-14. Additionally, Figures 2A-2E provide a sequence comparison illustrating differences among the different sequences.

The different sequences provided in the application are relevant to support the scope of the claims. "Prophetic examples are routinely used in chemical arts, and certainly can be sufficient to satisfy the written description requirements." *Ariad,* 598 F.3d at 1357, 94 USPQ2d at 1176.

Support for the different sequences described in the application being protective is provided by the ability of SEQ ID NO: 28 to provide protection against different clinical isolates. Such protection data illustrates that ORF0657n present in different organisms can be targeted, and provides evidence that the corresponding region from other *S. aureus* strains involved in generating an immune response (*e.g.,* ORF0657nI) could be used to provide protection.

With respect to SEQ ID NO: 1 and data provided in the application, included among the additional sequences are amino acids 1-442 of SEQ ID NO: 11; amino acids 1-442 of SEQ ID NO: 18; amino acids 1-445 of SEQ ID NO: 19; amino acids 1-454 of SEQ ID NO: 22; and amino acids 1-446 of SEQ ID NO: 24. (The present application at page 13, lines 3-13.) CL-10 corresponds to SEQ ID NO: 11, CL-13 corresponds to SEQ ID NO: 19, CL-18 corresponds to SEQ ID NO: 18, CL-21 responds to SEQ ID NO: 22, and CL30 corresponds to SEQ ID NO: 24.

The sequence identity provided in Table 3 for the full-length ORF0657n polypeptides and the results showing protection with different clinical isolates reasonably convey to one skilled in the art that applicants were in possession of the polypeptides described in the claims. Table 3 indicates a ranges of sequence identity of different clinical isolates of up to 94% to SEQ ID NO: 2. (The present application at pages 28-29.)

Additional support for an at least 94% sequence identity is provided by Figures 2A to 2E, which illustrate alterations among different clinical isolates. A 94% sequence identity to SEQ ID NO: 1 provides about 27 alterations. In the ORF0657nI region of SEQ ID NO: 1: CL-10 (SEQ ID NO: 11) has 10 alterations; CL-18 (SEQ ID NO: 18) has 10 alterations; CL-13 (SEQ ID NO: 19) has 7 alterations; CL-21 (SEQ ID NO: 22 has 22 alterations); and CL30 (SEQ ID NO: 24) has 11 alterations. (See the present application at Figures 2A-2E.[1]) The sequence identity for the 22 alterations is about 95% ([446-23]/446= 95.07 %)[2]. The combined number of unique

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[1] The alteration to SEQ ID NO: 1 is noted by the comparing highlighted regions in SEQ ID NO: 1 and other sequences, and also taking into account indicated gaps.

[2] The 446 amino acids used in the calculation is for the full-length SEQ ID NO: 1, which includes an amino terminal methionine. The sequence alignment provided in Figures 2A-2E does not show the amino acid corresponding to the

alterations for SEQ ID NOs: 11, 18, 19, 22 and 24 with respect to the ORF0657nI region of SEQ ID NO: 1 is 37 alterations. The sequence identity for the 37 alterations is about 92% ([446-37]/446).

4. Example 16: Additional Protection Data

Additional protection data using different constructs is provided by Example 16 of the application. (The present application at page 50, line 30 to page 51, line 21.) The results are shown in Figure 10. With respect to Figure 10, ORF0657nH (*E. coli*) corresponds to SEQ ID NO: 4 with a carboxyl His-Tag, ORF0657nI (*E. coli*) corresponds to SEQ ID NO: 5 with a carboxyl His-Tag, ORF0657nC (*E. coli*) corresponds to SEQ ID NO: 28; and ORF0657nH (yeast) corresponds to SEQ ID NO: 3. (The present application at page 7, lines 9-13.)

In the experiments illustrated in Figure 10, the polypeptide providing an ORF0657nI region generated a similar level of protection to the polypeptide providing the ORF0657nH region. It is respectfully submitted, the data provides additional evidence that ORF0657nH does not contain a critical region beyond that provided by the ORF0657nI region. While not indicated in the application, the challenge strain employed in Example 16 was *S. aureus* strain Becker.

5. Examiner's Comments

The rejection is improperly based on speculation concerning the potential impact of an unidentified mutation to a protective polypeptide, provides unsupported and incorrect statements concerning SEQ ID NO: 4 providing an example of a polypeptide consisting of an amino acid sequence 99.8% identical to SEQ ID NO: 1 which is not protective (see, for example, Arguments I.A.5.d., I.A.5.e., and I.A.5.f. *infra.)*; provides arguments regarding a fragment described in the application that is not within the scope of claims 1, 8, 9, and 38 (see, for example, Arguments I.A.5.d. and I.A.5.e. *infra.*); and refers to part of some additional data (see, for example Argument, I.A.5.f. and I.A.5.i.. *infra*).

The rejection fails to indicate why one skilled in the art would not in general expect polypeptides within at least 94% sequence identity to SEQ ID NO: 3 or containing a region with

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SEQ ID NO: 1 amino terminus methionine for all the sequences. The presence of an amino acid other than methionine in the corresponding position would lower the sequence identity.

at least 94% sequence identity to SEQ ID NO: 1 to provide protection. Such an expectation is relevant, for example, in evaluating whether the polypeptides illustrated in the application are representative of the claims.

The rejection also fails to properly take into account the data generated in the application. For example, the examiner ignores the data concerning longer-length constructs, arguing that such constructs are not themselves within the scope of the claims. Such arguments fail to consider the data provided in the application as a whole, including the presence in the longer-length construct of a core region shown to be protective.

The examiner's arguments with respect to written description are set forth in pages 7-16 of the Advisory Action mailed March 25, 2010. Additional comments directed to the examiner's arguments are provided below.

a. Advisory Action from the Middle of Page 7 to the Middle of Page 8

The examiner notes the elected species is SEQ ID NO: 1 and characterizes several claims. Claims 1(b) and 8(b) are indicated to require the polypeptide immunogen to minimally consist of a fragment of an amino acid sequence 94% identical to SEQ ID NO: 3, wherein the fragment comprises an amino acid sequence 94% identical to SEQ ID NO: 1. The claim 7 immunogen is interpreted to require a protective immune response. The examiner also indicates claim 1 does not specify to whom the protective immune response is provided, that any amino acid may be substituted, modified or deleted along the length of SEQ ID NO: 3 and/or SEQ ID NO: 1 as long as the polypeptide fragment retains the percent identity, with or without the "further up to 25 amino acids", and that the full-length ORF0657n is not encompassed by the claims.

Applicants are not clear what is meant by retaining the percent identity with or without the "further up to 25 amino acids". Claims 1, 8, 9 and 38 refer to "at least" 94% identity, some later claims refer to up to 25 amino acid alterations. With respect to percent identity, applicants acknowledge that such description would allow for additional amino acids.

With respect to the examiner's comment concerning to whom the claim 1 immunogen provides protection, applicants note that claim 1 is directed to a polypeptide immunogen and is not a method claim. The application illustrates the ability of polypeptide immunogens to provide protection.

b. Advisory Action Bottom of Page 8 to the Top of Page 9

The examiner appears to take the position that the data provided with SEQ ID NO: 28 is not relevant to the pending claim. The examiner's argument is based on SEQ ID NO: 28 not being within the scope of the claims. The examiner also indicates that SEQ ID NOs: 3, 4 and 5 are not 94% or 90% identical to SEQ ID NO: 1.

The comments provided by the examiner fail consider data provided in the application illustrating, for example, the ability of SEQ ID NO: 1 to provide protective immunity against strain Becker and the fact that SEQ ID NO: 28 is a longer-length sequence containing an SEQ ID NO: 1 ORF0657nI region. (See Arguments I.A.1. to I.A.4. *supra.*)

c. Advisory Action Middle of Page 9

The examiner agues that the ability of SEQ ID NOs: 4 and 5 to provide protective immunity against heterologous *S. aureus* Becker is not sufficiently representative of the claimed species and does not show a structure function correlation sufficient to support the genus. The examiner's comments fail to take into account the targeting of heterologous strains illustrated in the application. The examiner also fails to provide a rationale as to why a significant number of polypeptides within the claimed genus would not be protective.

The data generated with SEQ ID NO: 5 illustrate that the ORF0657nI region is sufficient to generate an immune response. The data using SEQ ID NOs: 4 and 5 in combination with data generated using SEQ ID NO: 28 against different clinical isolates demonstrate possession of representative species and also provide a sufficient structure function correlation. (See Arguments I.A.1. to I.A.4. *supra.*)

d. Advisory Action from the Bottom of Page 9 to the Top of Page 11

The examiner argues that the Office did show why a significant number of polypeptides within the scope of the claims would not provide protection. The examiner refers to the application indicating that SEQ ID NO: 2 consisting of amino acids 82-486 is not protective and is within claims 7 and 53, and argues that SEQ ID NO: 4 when having a His-Tag appears to show statistically insignificant protection.

To the extent the application illustrates that SEQ ID NO: 2 amino acids 82-486 does not provide protection, the indicated fragment is not covered by the claims 1, 8, 9 and 38. The referenced SEQ ID NO: 2 fragment is indicated by the examiner to provide a sequence identity of 91% to SEQ ID NO: 1. The 91% identity is outside the scope of the claims in the present rejection, which require the immunogen to be 94% identical to SEQ ID NO:1.[3]

No particular rationale or evidence is provided concerning the examiner's position on the significance of the data generated with the SEQ ID NO: 4 polypeptide. Data concerning SEQ ID NO: 4 is provided in Figures 3B and 10. Such data show a real and reproducible effect.

Applicants also note that SEQ ID NO: 4 corresponds to the ORF0657nH region and that SEQ ID NO: 5 corresponds to the ORF0657nI region. The examiner appears to be taking the position that the data with the shorter ORF0657nI is sufficient to provide protection, while the longer fragment is not. No rationale is provided by the examiner for such distinction.

e. Advisory Action Middle of 11 to Middle of Page 12

The examiner argues that applicants were not in possession of *S. aureus* strains containing naturally occurring ORF0657nI or ORF0657nH regions; the state of the art does not document the existence of such strains; without the knowledge whether ORF0657nI or ORF0657nH is buried in the cell wall it would not be predictable whether naturally occurring ORF0657nI or ORF0657nH are protective; the employed polypeptides have not been tested for homologous protection and therefore it is not predictable that the corresponding ORF0657nI or ORF0657nH region from CL-11, CL-13, CL-18, and CL-21 would provide protection in a homologous strain; and again refers to SEQ ID NO: 2 amino acids 82-486 not being protective.

The examiner's arguments concerning the state of the art fail to take into account the teaching and guidance provided in the present application. The present application provides data demonstrating polypeptides corresponding to ORF657nI and ORF0657nH regions are sufficient to generate a protective immune response. Such data demonstrates that the target polypeptide is accessible to an immune response generated with polypeptides providing ORF657nI or ORF0657nH regions.

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[3] The SEQ ID NO: 2 fragment consisting of amino acids 82-486 also appears to be outside the scope of claim 53.

The present application provides different examples of naturally occurring ORF0657nI and ORF0657nH sequences. (See, for example, the present application Figures 2A-2E.)

Polypeptides providing protection in heterologous protection experiments would be expected to provide protection when used in a homologous challenge. The expectation is based on a homologous challenge experiment involving an immunogen having a polypeptide region that is the same a region present on the challenge strain, as opposed to a heterologous challenge where the immunogen has a different region than that present on the challenge strain.

Given the success of the heterologous challenge experiments described in the application, the examiner fails to provide a rationale or evidence as to why the skilled artisan would not expect the corresponding ORF0657nI or ORF0657nH region from other *S. aureus* strains such as CL-11, CL-13, CL-18, and CL-21 to provide protection in a homologous challenge.

To the extent the application illustrates that SEQ ID NO: 2 amino acids 82-486 does not provide protection, the referenced fragment is not covered by claims 1, 8, 9 and 38. SEQ ID NO: 2 amino acids 82-486 is indicated by the examiner to provide a sequence identity of 91% to SEQ ID NO: 1.

f. Advisory Action Middle of Page 12 to Top of Page 13

The examiner notes that the percent identity recited in the instant claims is relative to SEQ ID NO: 1, not SEQ ID NO: 2; indicates that CL-10, CL-13, CL-30, CL-18, and CL-21 sequences do not constitute polypeptide immunogen species consisting of an amino acid sequence 94% identical to SEQ ID NO: 1 or immunogen species consisting of an amino acid sequence 90% identical to SEQ ID NO: 1 with up to 20 additional amino acids at its carboxyl or amino termimus; and that the corresponding regions of these sequences do not constitute polypeptides with an amino acid sequence 94% or 90% identical to SEQ ID NO: 1. The examiner argues that no sequence from CL-10, CL-13, CL-30, CL-18, and CL-21 has been correlated with homologous or heterologous protection, the results with SEQ ID NO: 2 amino acids 82-486 show no protection; the results with SEQ ID NO: 4 are not significant; and refers to additional data illustrating a lack of protection for ORF0657nI in the absence of endotoxin.

The "at least 94% identity" to SEQ ID NO: 1 is supported by the expectation that polypeptides having a high degree of structural similarity to SEQ ID NO: 1 would be able to provide protection, and by data described in the application along with the sequence comparison

provided in Figures 2A to 2E. The examiner fails to provide any rationale or evidence as to why the skilled artisan would not expect the corresponding ORF0657nI or ORF0657nH region from other *S aureus* strains such as CL-10, CL-13, CL-30, CL-18, and CL-21 to provide protection in a homologous challenge. Indeed, the skilled artisan would expect the corresponding regions from strains such as CL-10, CL-13, CL-30, CL-18, and CL-21, when used as an immunogen in a homologous challenge, would provide protection based on providing a region with the same sequence as actually present in the challenge organism.

The examiner argues for unpredictability based on the data provided with SEQ ID NO: 2 amino acids 82-486 and SEQ ID NO: 4. The referenced SEQ ID NO: 2 fragment is not covered by the claims 1, 8, 9 and 38.

In arguing unpredictability based on SEQ ID NO: 4, the examiner asserts that the SEQ ID NO: 4 polypeptide does not provide statistically significant protection, despite an identity of 99.8% SEQ ID NO: 1. No particular rationale or evidence is provided concerning the examiner's position on the significance the data using the SEQ ID NO: 4 polypeptide. Data concerning SEQ ID NO: 4 is provided in Figures 3B and 10. Such data show a real and reproducible effect.

Additionally, SEQ ID NO: 4 corresponds to the ORF0657nH region and SEQ ID NO: 5 corresponds to the ORF0657nI region. The examiner appears to be taking the position that the data with the shorter ORF0657nI is sufficient to provide protection, while the longer fragment is not. No rationale is provided by the examiner for such distinction.

With respect to the additional data, applicants assume the examiner is referring to an Amendment filed August 18, 2009. (See Examiner's comments in section (i) *infra.*) The August 18, 2009 amendment provides data indicating variability in the model employed and that an immune response could be produced in the absence of endotoxin. The endotoxin was shown to have an effect in the BALB/C mice model. The August 18, 2009 amendment also indicates that yeast produced ORF0657nI not containing endotoxin provided protective immunity in ICR Mice.

g. Advisory Action Page 13 Second Full Paragraph

The examiner indicates no requirement was made that the claimed polypeptides provide protection against each and every *S. aureus* in a non-human or human host and that von Eiff *et al.* (*Diagn. Microbiol. Infect. Dis.* 58:297-302, 2007) was properly cited by the Patent Office to

document the existence of immunologically heterogeneous or distinct types among *S. aureus*. It was applicants understanding that the von Eiff *et al.* reference was previously cited to support an argument that the present polypeptides need to provide protection against homologous or heterologous strain, serotype, *Spa* type, phage type or capsular type of *S. aureus*. (Office Action dated November 24, 2009, at page 9).

Applicants appreciate the examiner acknowledging that protection need not be shown against every *S. aureus* strain. Applicants' prior comments with respect to von Eiff *et al.* noted that the reference did not concern the presence of ORF0657n.

h. Advisory Action Page 13, Third Full Paragraph

The examiner indicates the Becker sequence is not covered by the instant claims, at the time the application was filed applicants were not in possession of the Becker sequence, and refers to a conversation with applicant's representative indicating that the Becker ORF0657n sequence is not part of the instant application.

In the telephone conversation referred to by the examiner, applicants' representative indicated that the Becker sequence was not provided in the application. The conversation did involve the question as to whether applicants were in possession of the Becker sequence at the time the application was filed.

S. aureus strain Becker is a laboratory strain of *S. aureus*, as opposed to *S. aureus* obtained from a clinical isolate. (See the present application at Table 3 pages 28 and 29.) The present application indicates the ORF0657n strain Becker sequence has a sequence identity to SEQ ID NO: 2 of 95%. (The present application in Table 3, on page 29.) The application reasonably conveys to the skilled artisan that applicants had possession of the strain Becker ORF0657 sequence.

i. Advisory Action Bottom of Page 13 to Top of Page 14

The examiner argues the issue of host species in which protection is to be provided is very relevant in light of Applicants' data. According to the examiner, based on data submitted in Amendment/Remarks filed June August 18, 2008, ORF0657nI would not be expected to provide protection in a human patient on its own including an immunodeficient, immunosuppressed and immunocompromised patent.

Reference to immunodeficient, immunosuppressed and immunocompromised patients appears to be an argument that applicants must show possession of a polypeptide that provides protective immunity in a patient lacking the ability to induce an immune response. Given the teaching in the application concerning use of the polypeptides to provide protective immunity, the skilled artisan could readily employ the polypeptide in a host having a functioning immune system to respond to the immunogen.

The claims in question are directed to immunogens and pharmaceutical compositions. How a particular immunogen is used goes to enablement of a method of use. Given the examples provided in the application using animal models, additional effectiveness in a non-human or human (e.g., immunodeficient, immunosuppressed and immunocompromised patient) does not need to be shown. As the rejection appears to be based on enablement for certain uses, applicants note that: "The enablement requirement is met if the description enables any mode of making and using the claimed invention." *Engel Industries Inc. v. The Lockformer Co.* 946 F.2d 1528, 1533, 20 USPQ2d 1300, 1304 (Fed. Cir. 1991).

With respect to the additional data provided in the August 18, 2009 amendment, the data indicates variability in the model employed and that an immune response could be produced in the absence of endotoxin. The endotoxin was attributed to have an effect in the BALB/C mice model. The August 18, 2009 amendment also indicates that yeast produced ORF0657nI not containing endotoxin provided protective immunity in ICR Mice.

j. Advisory Action from the Bottom of Page 14 to the Bottom of Page 16

The examiner notes that alterations to SEQ ID NO: 1 encompasses alterations, substitutions and deletions within SEQ ID NO: 1, argues that the Office has previously established the polypeptides having any degree of structural similarity are not necessarily expected to have similar properties absent a concrete structure-function correlation, and cites Colman P.M. (*Research Immunol.* 145:33-36, 1994), McGuiness *et al.,* (*Mol. Microbiol.* 7:505-514, Feb 1993), and McGuiness *et al.*, (*Lancet* 337:514-517, March 1991) for the argument that a change of a single amino acid can disrupt antibody-polypeptide binding.

The references concerning antibody-peptide interactions are silent as to the likelihood that a particular alteration would prevent a longer-length polypeptide, shown to be protective,

from maintaining its ability to provide protection. The possibility that some unknown alteration in an amino acid residue may impact a particular protein-antibody interaction, does not equate to a significant number of polypeptides within the scope of the claims losing its ability to provide protective immunity.

The rejection takes the position that if a single unidentified alteration within the 446 amino acids of SEQ ID NO: 1 may render the polypeptide not protective, then written description is lacking. Such an argument fails to consider what is reasonably conveyed to the skilled artisan by the percent of polypeptides within the described genus that are active.

Furthermore, SEQ ID NO: 1 is 446 amino acids in length and may contain more than one epitope providing a beneficial effect. Epitopes providing beneficial effects could include one or more B-cell epitopes and one or more T-cell epitopes. The T-cell epitopes would drive a cell mediated response involving the presentation of short antigens on antigen presenting cells.

In contrast to speculations provided by the examiner concerning the possible impact of alterations, the present application provides evidence using heterologous protection studies that alterations could be made where the resulting polypeptide is protective. (See Arguments I.A.1. to I.A.4. *supra*.)

B. The Data and Guidance in the Application Provides Written Description Support for Claim 4

Claim 4 further describes the polypeptide immunogen of claim 1 by indicating that the immunogen consists of an amino acid sequence at least 94% identical to SEQ ID NO: 1, SEQ ID NO: 3 or SEQ ID NO: 42. SEQ ID NO: 3 provide an ORF0657nH region and SEQ ID NO: 42 provides an ORF0657nI+ region. (See Figure 1 of the application.)

The Patent Office rejection does not provide any additional basis for rejecting claim 4 as opposed to claim 1. The rejection appears to be based on reference to at least 94% identical to SEQ ID NO: 1.

As discussed in Argument I. *supra.,* the application provides sufficient written description support for at least 94% identical to SEQ ID NO: 1. To the extent the rejection to claim 4 is based on reference in the claim to 94% identical to SEQ ID N: 42, different ORF0657nI+ sequences are referenced in the application on page 13, line 28 to page 14, line 5.

C. The Data and Guidance in the Application Provide Written Description Support for Claims 33, 39, 40, and 49

Claims 33, 39, 40, and 49 further describe the polypeptide immunogen by indicating that the immunogen has up to 25 amino acid alterations from SEQ ID NO: 1. The rejection does not specially present arguments concerning 25 amino acid alterations, but rather takes the position that any number of alterations from SEQ ID NO: 1 lacks written description. As discussed in Argument I.A. *supra.,* the application provides sufficient written description support for at least 94% identical to SEQ ID NO: 1, which would encompass up to 25 amino acid alterations.

Additionally, the description of 25 alterations provides for a stronger structural relationship to polypeptides shown to be protective then the at least 94% identity. The stronger structural relationship to polypeptides such as SEQ ID NO: 1 and corresponding ORF0657nI regions illustrated in the application, provides additional support for the polypeptides being representative of the genus.

The examiner fails to provide evidence as to why the skilled artisan would expect a significant number of polypeptides having up to 25 alterations from SEQ ID NO: 1 not to be protective. In contrast, the present application provides evidence using heterologous protection studies that alterations could be made where the resulting polypeptide is protective. (See Argument I.A. *supra.*)

Additional support for up to 25 alterations is provided in the application by Figures 2A to 2E. Figures 2A to 2E illustrate different examples of amino acid alterations occurring throughout the ORF0657nI and ORF0657nH regions. For example, in the ORF0657nI region CL-10 (SEQ ID NO: 11) has 10 alterations; CL-18 (SEQ ID NO: 18) has 10 alteration; CL-13 (SEQ ID NO: 19) has 7 alterations; CL-21 (SEQ ID NO: 22) has 22 alterations; and CL30 (SEQ ID NO: 24) has 11 alterations. The combined number of unique alterations for SEQ ID NOs: 11, 18, 19, 22 and 24 with respect to the ORF0657nI region of SEQ ID NO: 1 is 37 alterations. The consideration of additional strains further increases the number of illustrated alterations.

D. The Data and Guidance in the Application Provides Written Description Support for Claims 34, 41, 42, and 50

Claims 34, 41, 42, and 50 further describe the polypeptide immunogen by providing for up to 10 amino acid alterations from SEQ ID NO: 1. The rejection does not specially present an

argument concerning 10 amino acid alterations, but rather takes the position that any number of alterations from SEQ ID NO: 1 lacks written description. As discussed in Argument I.A. *supra.,* the application provides sufficient written description support for at least 94% identical to SEQ ID NO: 1, which encompasses up to 10 amino acid alterations.

Additionally, the description of 10 alterations provides for a stronger structural relationship to polypeptides shown to be protective then the at least 94% identity. The stronger structural relationship to polypeptides such as SEQ ID NO: 1 and corresponding ORF0657nI regions illustrated in the application, provides additional support for the polypeptides being representative of the genus.

The examiner fails to provide evidence as to why the skilled artisan would expect a significant number of polypeptides having up to 10 alterations from SEQ ID NO: 1 not to be protective. In contrast, the present application provides evidence using heterologous protection studies that alterations could be made where the resulting polypeptide is protective. (See Argument I.A. *supra.*)

Additional support for up to 10 alterations is provided in the application by Figures 2A to 2E. Figures 2A to 2E illustrate different examples of amino acid alterations occurring throughout the ORF0657nI and ORF0657nH regions. For example, in the ORF0657nI region CL-10 (SEQ ID NO: 11) has 10 alterations; CL-18 (SEQ ID NO: 18) has 10 alteration; CL-13 (SEQ ID NO: 19) has 7 alterations; CL-21 (SEQ ID No: 22) has 22 alterations; and CL30 (SEQ ID NO: 24) has 11 alterations.

E. The Data and Guidance in the Application Provide Written Description Support for Claims 35, 43, 44, and 51

Claims 35, 43, 44, and 51 further describe the polypeptide immunogen by providing for up to 5 amino acid alterations from SEQ ID NO: 1. The rejection does not specially present arguments concerning 5 amino acid alterations, but rather takes the position that any number of alterations from SEQ ID NO: 1 lacks written description. As discussed in Argument 1.A. *supra.,* the application provides sufficient written description support for at least 94% identical to SEQ ID NO: 1, which would encompass up to 5 amino acid alterations.

Additionally, the description of 5 alterations provides for a stronger structural relationship to polypeptides shown to be protective then the at least 94% identity. The stronger

structural relationship to polypeptides such as SEQ ID NO: 1 and corresponding ORF0657nI regions illustrated in the application, provides additional support for the polypeptide being representative of the genus.

The examiner fails to provide evidence as to why the skilled artisan would expect a significant number of polypeptides having up to 5 alterations from SEQ ID NO: 1 not to be protective. In contrast, the present application provides evidence using heterologous protection studies that alterations could be made where the resulting polypeptide is protective. (See Argument I.A. *supra*.)

Additional support for up to 5 alterations is provided in the application by Figures 2A to 2E. Figures 2A to 2E illustrate different examples of amino acid alterations occurring throughout the ORF0657nI and ORF0657nH regions. For example, in the ORF0657nI region CL-10 (SEQ ID NO: 11) has 10 alterations; CL-18 (SEQ ID NO: 18) has 10 alteration; CL-13 (SEQ ID NO: 19) has 7 alterations; CL-21 (SEQ ID NO: 22) has 22 alterations; and CL30 (SEQ ID NO: 24) has 11 alterations.

F. The Data and Guidance in the Application Provides Written Description Support for Claim 7

Claim 7 is directed to an immunogen consisting of an amino acid sequence at least 90% identical to SEQ ID NO: 1 and one or more additional regions or moieties covalently joined to the sequence at the carboxyl terminus or the amino terminus. Support for the at least 90% identity is provided in Figures 2A-2E. The ORF0657nI region in Figures 2A-2E goes from amino acid 3 to amino acid 455 and illustrates examples of differences between SEQ ID NO: 1 and different naturally occurring sequences. Adding the total differences between SEQ ID NO: 1 and the other strains provides for 49 unique differences.

Dividing 49 by the overall size of SEQ ID NO: 1 (446 amino acids) illustrates a sequence identity of 89%, which provides for a greater variation that the "at least 90%" sequence identity.[4]

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[4] The 446 amino acids used in the calculation is for the full-length SEQ ID NO: 1, which includes an amino terminal methionine. The sequence alignment provided in Figures 2A-2E does not show the amino acid corresponding to the SEQ ID NO: 1 amino terminus methionine for all the sequences. The presence of an amino acid other than methionine in the corresponding position would lower the sequence identity.

The heterologous protection data provided in the application illustrates that alterations could be made to SEQ ID NO: 1 and the resulting polypeptide would be protective.

With respect to claim 7, the examiner argues that SEQ ID NO: 2 amino acids 82-486 has a sequence identity of 91% to SEQ ID NO: 2 and does not provide protection. (See for example, Advisory Action dated March 24, 2010 at page 10.). To the extent that fragment is not protective, such a fragment is at the outer limit of claim 7 and is functionally excluded by the claim.

II. Claim 8 Complies With 35 U.S.C. § 112, Second Paragraph (Definiteness)

Claim 8 is alleged to be vague and indefinite based on reference to "composition *able to induce a protective immune response against S. aureus in a patient* comprising an *immunologically effective amount of* a purified polypeptide *that provides protective immunity against S. aureus".* The examiner argues that the later description of "provides protective immunity against *S. aureus"* does not reference --in said patient-- and therefore encompasses protective immunity against a non-patient or a patient other than recited in line 2 of the claim.

Definiteness under 35 U.S.C. 112, second paragraph, is determined based on whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986).

Claim 8 is a composition claim, not a method of use claim. The preamble description of a patient indicates a possible use of the composition and is not a limitation necessitating the use of the immunogen in a patient. Reference to providing protective immunity against *S. aureus* in the body of the claim refers to a property of the composition consistent with the claim preamble. The body of the claim also refers to a pharmaceutically acceptable carrier as part of the composition.

The skilled artisan reviewing the specification would readily understand that when the composition is used, the production of an immune response is to occur in the patient in which the immunogen is administered. For example, the application on page 7, line 34 to page 8, line 1 mentions protective immunity using an animal model. Additionally, the examples described in the application illustrate an immune response in an animal model to which the immunogen was

added. (See, for example, Example 3 on page 26, line 17 to page 27, line 2; Example 6 on page 29, lines 10-21; and Example 16 on page 50, line 30 to page 51, line 22.)

The examiner's position that the claims cover a composition that when administered to one patient, produces an effect in a second patient, is contrary to the present application and the plain wording of the claim.

III. Claim 7 Complies with 35 U.S.C. § 112, Second Paragraph (Definiteness)

Claim 7 is indicated to be vague and indefinite based on reference to "facilitates polypeptide stability". The examiner indicates that it is unclear the stability of which polypeptide is being facilitated by the one or more additional regions or moieties. The examiner notes the claim has no earlier recitation of any polypeptide, and the claimed immunogen is not purified and may be in an environment with extraneous polypeptide in major or residual amount. The examiner inquires whether the description refers to a situation where the claimed immunogen is unpurified in association with an unclaimed polypeptide and the stability of the unclaimed polypeptide is facilitated.

Reference to "facilitates polypeptide stability" provided in claim 7 clearly refers to a property of the additional region or moiety, where the additional region or moiety is joined to said sequence. Claim 7 asserts:

> 7. An immunogen consisting of an amino acid **sequence** at least 90% identical to SEQ ID NO: 1 and one or more **additional regions or moieties covalently joined to said sequence** at the carboxyl terminus or the amino terminus, wherein **each of said one or more additional regions or moieties is independently selected** from a region or moiety having at least one of the following properties: enhances the immune response, facilitates purification, or facilitates polypeptide stability. (Emphasis added.)

Properties of additional regions or moieties are listed in a Markush group. One of the indicated properties is facilitates polypeptide stability. The additional region or moieties is joined to said sequence.

IV. Claims 9 and 38-54 Comply with 35 U.S.C. § 112, Second Paragraph (Definiteness)

Claims 9 and 38-54, which depend directly or indirectly from claims 7 or 8, are rejected as allegedly indefinite. The rejection is based on claims 7 and 8 allegedly being indefinite. For

this rejection, the claims are argued in separate groups based on the claim dependency: (A) claims 9 and 38-48; and (B) claims 49-54.

A. Claims 9 and 38-48

Claims 9 and 38-48 stand rejected based on their dependency from claim 8. As discussed in Argument II. *supra*. claim 8 is not indefinite.

B. Claims 49-54

Claims 49-54 stand rejected based on their dependency from claim 7. As discussed in Argument III. *supra*. claim 7 is not indefinite.

V. Claims 5 and 6 Stand Objected as Covering a Non-Elected and Non-Searched Species

The examiner indicates that claims 5 and 6 cover non-elected species and that a search and further consideration of the non-elected species is needed. Claims 5 and 6 refer to SEQ ID NO: 1, 3, 7, 17, 20, or 42.

The provided objection appears to be based on the argument that the generic description covering the non-elected species is allegedly not patentable. Applicants note that the prior office action did not object to the subject matter of claims 5 and 6.

As discussed in Argument I.A. *supra*, claim 1 is allowable. The general polypeptide description provided for in claim 1 covers the polypeptides species listed in claims 5 and 6. Claims 5 and 6 do not specifically refer to "purified", however no objection to these claims was provided on that basis. Accordingly, the objection to claims 5 and 6 should be removed.

VI. Claim 36 Stands Objected for Depending Upon Claim 6

Claim 36 was indicated to be allowable if rewritten in dependent form including all the limitations of the base claim and any intervening claim. Claim 36 depends from claim 6. As discussed in Argument V. *supra*., the objection to claim 6 showed be removed.

CONCLUSION

Appellants request that the Board of Patent Appeals and Interferences reverse the outstanding rejections of claims 1, 4, 7-9, 33-35, and 38-54 and the objections to claims 5, 6, and 36.

Please charge deposit account 13-2755 for fees due in connection with this Appeal Brief. If any time extensions are needed for the timely filing of the present Appeal Brief, Appellants petition for such extensions and authorize the charging of deposit account 13-2755 for the appropriate fees.

Respectfully submitted,

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CLAIMS APPENDIX

Claim 1. A purified polypeptide immunogen consisting of either (a) an amino acid sequence at least 94% identical to SEQ ID NO: 3, or (b) a fragment of said amino acid sequence at least 94% identical to SEQ ID NO: 3, wherein said fragment comprises an amino acid sequence at least 94% identical to SEQ ID NO: 1; wherein said polypeptide immunogen provides protective immunity against *S. aureus*.

Claim 4. The polypeptide immunogen of claim 1, wherein said polypeptide immunogen consists of an amino acid sequence at least 94% identical to SEQ ID NO: 1, SEQ ID NO: 3 or SEQ ID NO: 42.

Claim 5. A polypeptide immunogen consisting of the amino acid sequence of SEQ ID NO: 1, 3, 7, 17, 20, or 42, each with up to 20 additional amino acids, wherein the up to 20 additional amino acids can be located at the carboxyl or the amino terminus.

Claim 6. The polypeptide immunogen of claim 5 wherein said polypeptide immunogen consists of the amino acid sequence of SEQ ID NO: 1, 3, 7, 17, 20, or 42.

Claim 7. An immunogen consisting of an amino acid sequence at least 90% identical to SEQ ID NO: 1 and one or more additional regions or moieties covalently joined to said sequence at the carboxyl terminus or the amino terminus, wherein each of said one or more additional regions or moieties is independently selected from a region or moiety having at least one of the

following properties: enhances the immune response, facilitates purification, or facilitates polypeptide stability.

Claim 8. A composition able to induce a protective immune response against *S. aureus* in a patient comprising an immunologically effective amount of a purified polypeptide immunogen that provides protective immunity against *S. aureus* and a pharmaceutically acceptable carrier, wherein the polypeptide immunogen consists of either (a) an amino acid sequence at least 94% identical to SEQ ID NO: 3, or (b) a fragment of said amino acid sequence at least 94% identical to SEQ ID NO: 3, where said fragment comprises an amino acid sequence at least 94% identical to SEQ ID NO: 1.

Claim 9. The composition of claim 8, wherein said composition further comprises an adjuvant.

Claim 33. The polypeptide immunogen of claim 1, wherein said polypeptide immunogen is SEQ ID NO: 1 or differs from SEQ ID NO: 1 by up to 25 amino acid alterations.

Claim 34. The polypeptide immunogen of claim 33, wherein said polypeptide immunogen is SEQ ID NO: 1 or differs from SEQ ID NO: 1 by up to 10 amino acid alterations.

Claim 35. The polypeptide immunogen of claim 34, wherein said polypeptide immunogen is SEQ ID NO: 1 or differs from SEQ ID NO: 1 by up to 5 amino acid alterations.

Claim 36. The polypeptide immunogen of claim 6, wherein said polypeptide immunogen is SEQ ID NO: 1.

Claim 38. The composition of claim 8, wherein said polypeptide immunogen is substantially purified and said patient is a human.

Claim 39. The composition of claim 8, wherein said polypeptide immunogen is SEQ ID NO: 1 or differs from SEQ ID NO: 1 by up to 25 amino acid alterations.

Claim 40. The composition of claim 39, wherein said polypeptide immunogen is substantially purified and said patient is a human.

Claim 41. The composition of claim 8, wherein said polypeptide immunogen is SEQ ID NO: 1 or differs from SEQ ID NO: 1 by up to 10 amino acid alterations.

Claim 42. The composition of claim 41, wherein said polypeptide immunogen is substantially purified and said patient is a human.

Claim 43. The composition of claim 8, wherein said polypeptide immunogen is SEQ ID NO: 1 or differs from SEQ ID NO: 1 by up to 5 amino acid alterations.

Claim 44. The composition of claim 43, wherein said polypeptide immunogen is substantially purified and said patient is a human.

Claim 45. The composition of claim 8, wherein said polypeptide immunogen is SEQ ID NO: 1.

Claim 46. The composition of claim 45, wherein said polypeptide immunogen is substantially purified and said patient is a human.

Claim 47. The composition of claim 8, wherein said polypeptide immunogen consists of the amino acid sequence of SEQ ID NO: 1, 3, 7, 17, 20, or 42, each with up to 20 additional amino acids, wherein the up to 20 additional amino acids can be located at the carboxyl or the amino terminus.

Claim 48. The composition of claim 47, wherein said polypeptide immunogen consists of the amino acid sequence of SEQ ID NO: 1, 3, 7, 17, 20, or 42.

Claim 49. The immunogen of claim 7, wherein said amino acid sequence is SEQ ID NO: 1 or differs from SEQ ID NO: 1 by up to 25 amino acid alterations.

Claim 50. The immunogen of claim 49, wherein said amino acid sequence is SEQ ID NO: 1 or differs from SEQ ID NO: 1 by up to 10 amino acid alterations.

Claim 51. The immunogen of claim 50, wherein said amino acid sequence is SEQ ID NO: 1 or differs from SEQ ID NO: 1 by up to 5 amino acid alterations.

Claim 52. The immunogen of claim 51, wherein said amino acid sequence is SEQ ID NO: 1.

Claim 53. The immunogen of claim 7, wherein said amino acid sequence consists of SEQ ID NO: 1, 3, 7, 17, 20, or 42, each with up to 20 additional amino acids, wherein the up to 20 additional amino acids can be located at the carboxyl or the amino terminus.

Claim 54. The immunogen of claim 53, wherein said amino acid sequence consists of SEQ ID NO: 1, 3, 7, 17, 20, or 42.

EVIDENCE APPENDIX

Exhibit 1 - Exhibit 1 is the same as Appendix A filed with Applicants' response dated February 24, 2010. Appendix A (Exhibit 1) was entered by the examiner in the Advisory action dated March 25, 2010.

Exhibit 2 - Exhibit 2 is the same as Appendix B filed with Applicants' response dated February 24, 2010. Appendix B (Exhibit 2) was entered by the examiner in the Advisory action dated March 25, 2010.

Exhibit A

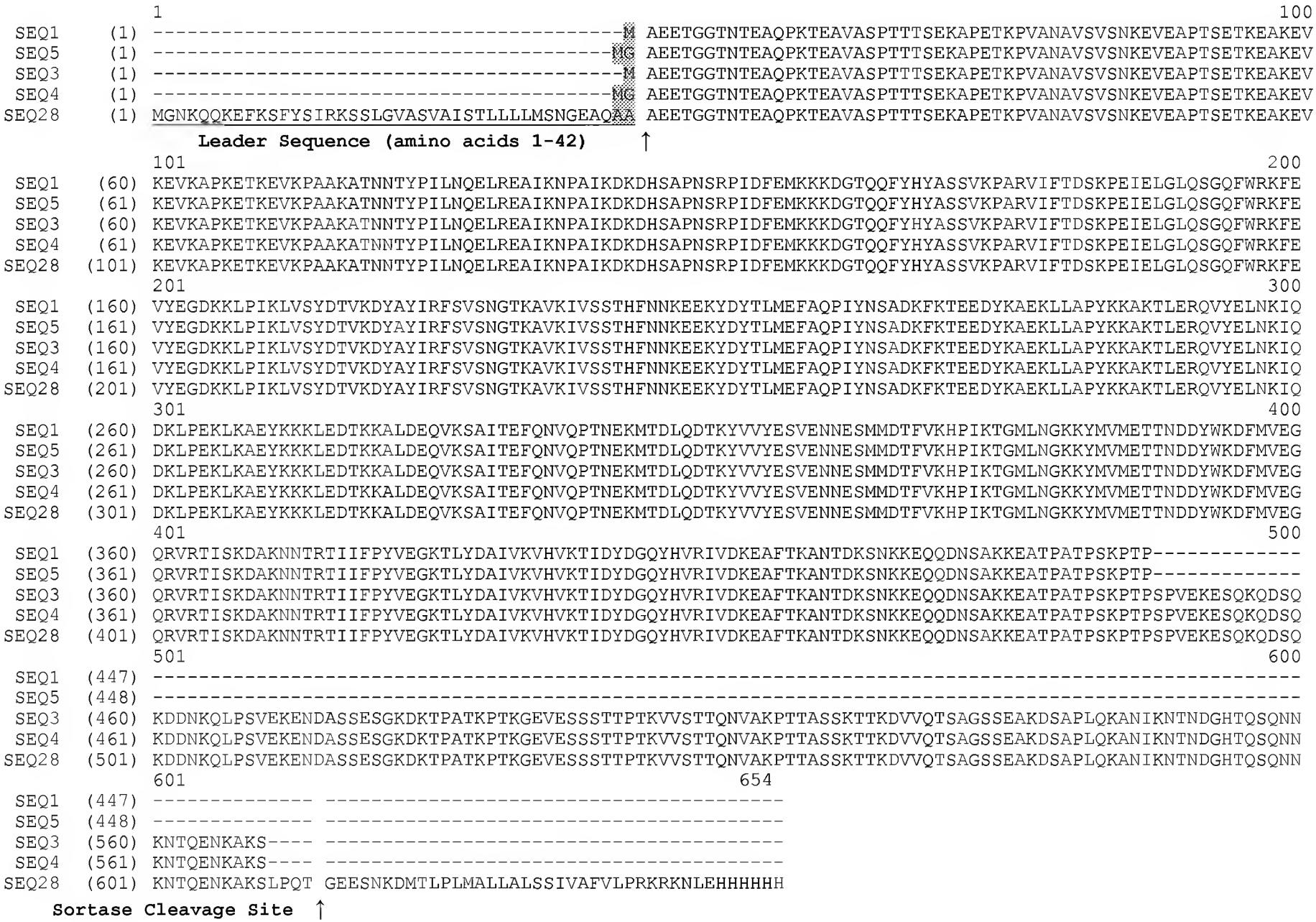
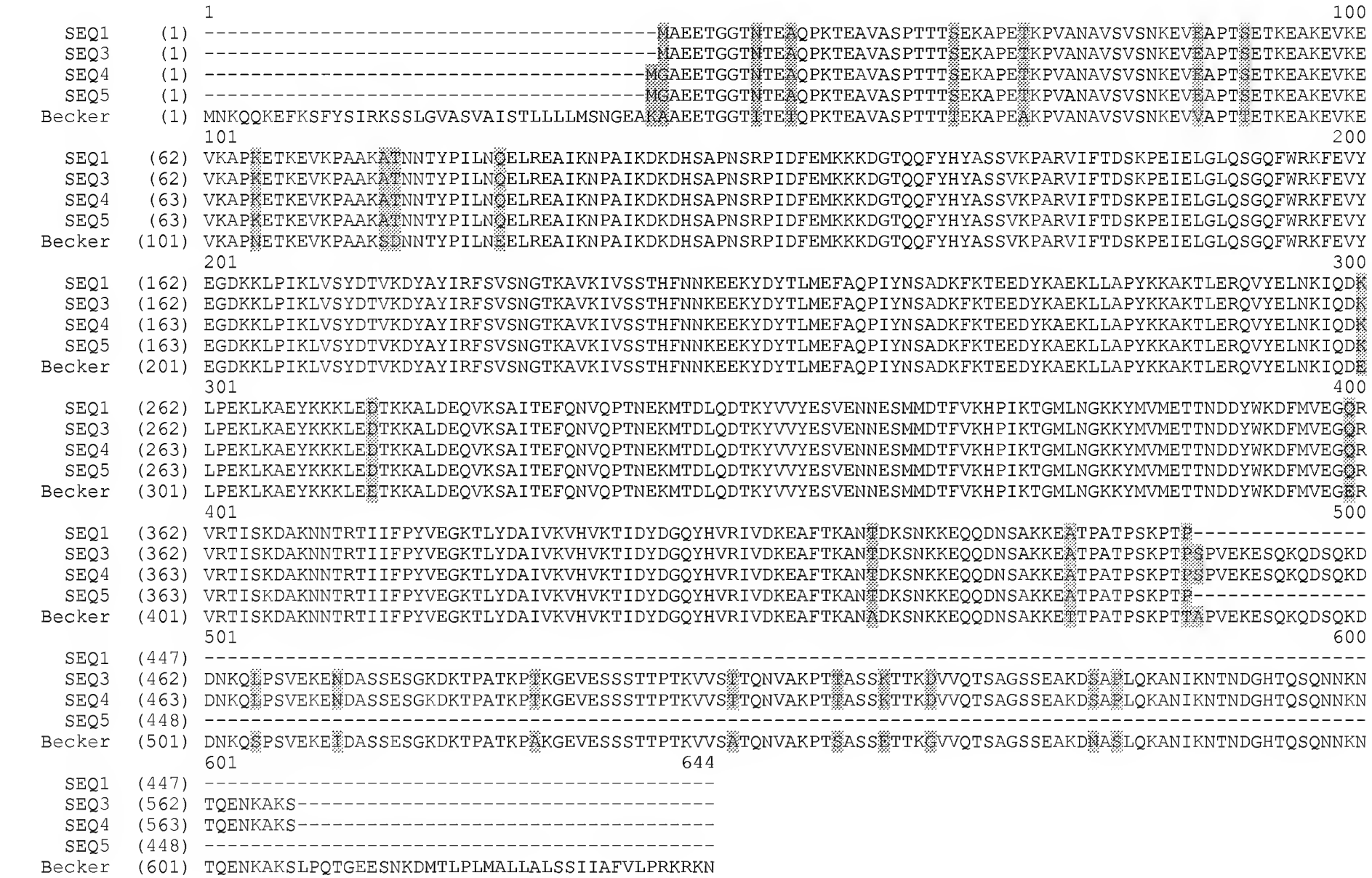

1 100
SEQ1 (1) ----------M AEETGGTNTEAQPKTEAVASPTTTSEKAPETKPVANAVSVSNKEVEAPTSETKEAKEV
SEQ5 (1) ----------MG AEETGGTNTEAQPKTEAVASPTTTSEKAPETKPVANAVSVSNKEVEAPTSETKEAKEV
SEQ3 (1) ----------M AEETGGTNTEAQPKTEAVASPTTTSEKAPETKPVANAVSVSNKEVEAPTSETKEAKEV
SEQ4 (1) ----------MG AEETGGTNTEAQPKTEAVASPTTTSEKAPETKPVANAVSVSNKEVEAPTSETKEAKEV
SEQ28 (1) MGNKQQKEFKSFYSIRKSSLGVASVAISTLLLLMSNGEAQAA AEETGGTNTEAQPKTEAVASPTTTSEKAPETKPVANAVSVSNKEVEAPTSETKEAKEV
Leader Sequence (amino acids 1-42)
101 200
SEQ1 (60) KEVKAPKETKEVKPAAKATNNTYPILNQELREAIKNPAIKDKDHSAPNSRPIDFEMKKKDGTQQFYHYASSVKPARVIFTDSKPEIELGLQSGQFWRKFE
SEQ5 (61) KEVKAPKETKEVKPAAKATNNTYPILNQELREAIKNPAIKDKDHSAPNSRPIDFEMKKKDGTQQFYHYASSVKPARVIFTDSKPEIELGLQSGQFWRKFE
SEQ3 (60) KEVKAPKETKEVKPAAKATNNTYPILNQELREAIKNPAIKDKDHSAPNSRPIDFEMKKKDGTQQFYHYASSVKPARVIFTDSKPEIELGLQSGQFWRKFE
SEQ4 (61) KEVKAPKETKEVKPAAKATNNTYPILNQELREAIKNPAIKDKDHSAPNSRPIDFEMKKKDGTQQFYHYASSVKPARVIFTDSKPEIELGLQSGQFWRKFE
SEQ28 (101) KEVKAPKETKEVKPAAKATNNTYPILNQELREAIKNPAIKDKDHSAPNSRPIDFEMKKKDGTQQFYHYASSVKPARVIFTDSKPEIELGLQSGQFWRKFE
201 300
SEQ1 (160) VYEGDKKLPIKLVSYDTVKDYAYIRFSVSNGTKAVKIVSSTHFNNKEEKYDYTLMEFAQPIYNSADKFKTEEDYKAEKLLAPYKKAKTLERQVYELNKIQ
SEQ5 (161) VYEGDKKLPIKLVSYDTVKDYAYIRFSVSNGTKAVKIVSSTHFNNKEEKYDYTLMEFAQPIYNSADKFKTEEDYKAEKLLAPYKKAKTLERQVYELNKIQ
SEQ3 (160) VYEGDKKLPIKLVSYDTVKDYAYIRFSVSNGTKAVKIVSSTHFNNKEEKYDYTLMEFAQPIYNSADKFKTEEDYKAEKLLAPYKKAKTLERQVYELNKIQ
SEQ4 (161) VYEGDKKLPIKLVSYDTVKDYAYIRFSVSNGTKAVKIVSSTHFNNKEEKYDYTLMEFAQPIYNSADKFKTEEDYKAEKLLAPYKKAKTLERQVYELNKIQ
SEQ28 (201) VYEGDKKLPIKLVSYDTVKDYAYIRFSVSNGTKAVKIVSSTHFNNKEEKYDYTLMEFAQPIYNSADKFKTEEDYKAEKLLAPYKKAKTLERQVYELNKIQ
301 400
SEQ1 (260) DKLPEKLKAEYKKKLEDTKKALDEQVKSAITEFQNVQPTNEKMTDLQDTKYVVYESVENNESMMDTFVKHPIKTGMLNGKKYMVMETTNDDYWKDFMVEG
SEQ5 (261) DKLPEKLKAEYKKKLEDTKKALDEQVKSAITEFQNVQPTNEKMTDLQDTKYVVYESVENNESMMDTFVKHPIKTGMLNGKKYMVMETTNDDYWKDFMVEG
SEQ3 (260) DKLPEKLKAEYKKKLEDTKKALDEQVKSAITEFQNVQPTNEKMTDLQDTKYVVYESVENNESMMDTFVKHPIKTGMLNGKKYMVMETTNDDYWKDFMVEG
SEQ4 (261) DKLPEKLKAEYKKKLEDTKKALDEQVKSAITEFQNVQPTNEKMTDLQDTKYVVYESVENNESMMDTFVKHPIKTGMLNGKKYMVMETTNDDYWKDFMVEG
SEQ28 (301) DKLPEKLKAEYKKKLEDTKKALDEQVKSAITEFQNVQPTNEKMTDLQDTKYVVYESVENNESMMDTFVKHPIKTGMLNGKKYMVMETTNDDYWKDFMVEG
401 500
SEQ1 (360) QRVRTISKDAKNNTRTIIFPYVEGKTLYDAIVKVHVKTIDYDGQYHVRIVDKEAFTKANTDKSNKKEQQDNSAKKEATPATPSKPTP----------
SEQ5 (361) QRVRTISKDAKNNTRTIIFPYVEGKTLYDAIVKVHVKTIDYDGQYHVRIVDKEAFTKANTDKSNKKEQQDNSAKKEATPATPSKPTP----------
SEQ3 (360) QRVRTISKDAKNNTRTIIFPYVEGKTLYDAIVKVHVKTIDYDGQYHVRIVDKEAFTKANTDKSNKKEQQDNSAKKEATPATPSKPTPSPVEKESQKQDSQ
SEQ4 (361) QRVRTISKDAKNNTRTIIFPYVEGKTLYDAIVKVHVKTIDYDGQYHVRIVDKEAFTKANTDKSNKKEQQDNSAKKEATPATPSKPTPSPVEKESQKQDSQ
SEQ28 (401) QRVRTISKDAKNNTRTIIFPYVEGKTLYDAIVKVHVKTIDYDGQYHVRIVDKEAFTKANTDKSNKKEQQDNSAKKEATPATPSKPTPSPVEKESQKQDSQ
501 600
SEQ1 (447) ----------
SEQ5 (448) ----------
SEQ3 (460) KDDNKQLPSVEKENDASSESGKDKTPATKPTKGEVESSSTTPTKVVSTTQNVAKPTTASSKTTKDVVQTSAGSSEAKDSAPLQKANIKNTNDGHTQSQNN
SEQ4 (461) KDDNKQLPSVEKENDASSESGKDKTPATKPTKGEVESSSTTPTKVVSTTQNVAKPTTASSKTTKDVVQTSAGSSEAKDSAPLQKANIKNTNDGHTQSQNN
SEQ28 (501) KDDNKQLPSVEKENDASSESGKDKTPATKPTKGEVESSSTTPTKVVSTTQNVAKPTTASSKTTKDVVQTSAGSSEAKDSAPLQKANIKNTNDGHTQSQNN
601 654
SEQ1 (447) ---------- ----------
SEQ5 (448) ---------- ----------
SEQ3 (560) KNTQENKAKS---- ----------
SEQ4 (561) KNTQENKAKS---- ----------
SEQ28 (601) KNTQENKAKSLPQT GEESNKDMTLPLMALLALSSIVAFVLPRKRKNLEHHHHHH
Sortase Cleavage Site

Exhibit B


1 100
SEQ1 (1) ----------MAEETGGTNTEAQPKTEAVASPTTTSEKAPETKPVANAVSVSNKEVEAPTSETKEAKEVKE
SEQ3 (1) ----------MAEETGGTNTEAQPKTEAVASPTTTSEKAPETKPVANAVSVSNKEVEAPTSETKEAKEVKE
SEQ4 (1) ----------MGAEETGGTNTEAQPKTEAVASPTTTSEKAPETKPVANAVSVSNKEVEAPTSETKEAKEVKE
SEQ5 (1) ----------MGAEETGGTNTEAQPKTEAVASPTTTSEKAPETKPVANAVSVSNKEVEAPTSETKEAKEVKE
Becker (1) MNKQQKEFKSFYSIRKSSLGVASVAISTLLLLMSNGEAKAAEETGGTITETQPKTEAVASPTTTTEKAPEAKPVANAVSVSNKEVVAPTTETKEAKEVKE
101 200
SEQ1 (62) VKAPKETKEVKPAAKATNNTYPILNQELREAIKNPAIKDKDHSAPNSRPIDFEMKKKDGTQQFYHYASSVKPARVIFTDSKPEIELGLQSGQFWRKFEVY
SEQ3 (62) VKAPKETKEVKPAAKATNNTYPILNQELREAIKNPAIKDKDHSAPNSRPIDFEMKKKDGTQQFYHYASSVKPARVIFTDSKPEIELGLQSGQFWRKFEVY
SEQ4 (63) VKAPKETKEVKPAAKATNNTYPILNQELREAIKNPAIKDKDHSAPNSRPIDFEMKKKDGTQQFYHYASSVKPARVIFTDSKPEIELGLQSGQFWRKFEVY
SEQ5 (63) VKAPKETKEVKPAAKATNNTYPILNQELREAIKNPAIKDKDHSAPNSRPIDFEMKKKDGTQQFYHYASSVKPARVIFTDSKPEIELGLQSGQFWRKFEVY
Becker (101) VKAPNETKEVKPAAKSDNNTYPILNEELREAIKNPAIKDKDHSAPNSRPIDFEMKKKDGTQQFYHYASSVKPARVIFTDSKPEIELGLQSGQFWRKFEVY
201 300
SEQ1 (162) EGDKKLPIKLVSYDTVKDYAYIRFSVSNGTKAVKIVSSTHFNNKEEKYDYTLMEFAQPIYNSADKFKTEEDYKAEKLLAPYKKAKTLERQVYELNKIQDK
SEQ3 (162) EGDKKLPIKLVSYDTVKDYAYIRFSVSNGTKAVKIVSSTHFNNKEEKYDYTLMEFAQPIYNSADKFKTEEDYKAEKLLAPYKKAKTLERQVYELNKIQDK
SEQ4 (163) EGDKKLPIKLVSYDTVKDYAYIRFSVSNGTKAVKIVSSTHFNNKEEKYDYTLMEFAQPIYNSADKFKTEEDYKAEKLLAPYKKAKTLERQVYELNKIQDK
SEQ5 (163) EGDKKLPIKLVSYDTVKDYAYIRFSVSNGTKAVKIVSSTHFNNKEEKYDYTLMEFAQPIYNSADKFKTEEDYKAEKLLAPYKKAKTLERQVYELNKIQDK
Becker (201) EGDKKLPIKLVSYDTVKDYAYIRFSVSNGTKAVKIVSSTHFNNKEEKYDYTLMEFAQPIYNSADKFKTEEDYKAEKLLAPYKKAKTLERQVYELNKIQDE
301 400
SEQ1 (262) LPEKLKAEYKKKLEDTKKALDEQVKSAITEFQNVQPTNEKMTDLQDTKYVVYESVENNESMMDTFVKHPIKTGMLNGKKYMVMETTNDDYWKDFMVEGQR
SEQ3 (262) LPEKLKAEYKKKLEDTKKALDEQVKSAITEFQNVQPTNEKMTDLQDTKYVVYESVENNESMMDTFVKHPIKTGMLNGKKYMVMETTNDDYWKDFMVEGQR
SEQ4 (263) LPEKLKAEYKKKLEDTKKALDEQVKSAITEFQNVQPTNEKMTDLQDTKYVVYESVENNESMMDTFVKHPIKTGMLNGKKYMVMETTNDDYWKDFMVEGQR
SEQ5 (263) LPEKLKAEYKKKLEDTKKALDEQVKSAITEFQNVQPTNEKMTDLQDTKYVVYESVENNESMMDTFVKHPIKTGMLNGKKYMVMETTNDDYWKDFMVEGQR
Becker (301) LPEKLKAEYKKKLEETKKALDEQVKSAITEFQNVQPTNEKMTDLQDTKYVVYESVENNESMMDTFVKHPIKTGMLNGKKYMVMETTNDDYWKDFMVEGER
401 500
SEQ1 (362) VRTISKDAKNNTRTIIFPYVEGKTLYDAIVKVHVKTIDYDGQYHVRIVDKEAFTKANTDKSNKKEQQDNSAKKEATPATPSKPTP----------
SEQ3 (362) VRTISKDAKNNTRTIIFPYVEGKTLYDAIVKVHVKTIDYDGQYHVRIVDKEAFTKANTDKSNKKEQQDNSAKKEATPATPSKPTPSPVEKESQKQDSQKD
SEQ4 (363) VRTISKDAKNNTRTIIFPYVEGKTLYDAIVKVHVKTIDYDGQYHVRIVDKEAFTKANTDKSNKKEQQDNSAKKEATPATPSKPTPSPVEKESQKQDSQKD
SEQ5 (363) VRTISKDAKNNTRTIIFPYVEGKTLYDAIVKVHVKTIDYDGQYHVRIVDKEAFTKANTDKSNKKEQQDNSAKKEATPATPSKPTP----------
Becker (401) VRTISKDAKNNTRTIIFPYVEGKTLYDAIVKVHVKTIDYDGQYHVRIVDKEAFTKANADKSNKKEQQDNSAKKETTPATPSKPTTAPVEKESQKQDSQKD
501 600
SEQ1 (447) ----------
SEQ3 (462) DNKQLPSVEKENDASSESGKDKTPATKPTKGEVESSSTTPTKVVSTTQNVAKPTTASSKTTKDVVQTSAGSSEAKDSAPLQKANIKNTNDGHTQSQNNKN
SEQ4 (463) DNKQLPSVEKENDASSESGKDKTPATKPTKGEVESSSTTPTKVVSTTQNVAKPTTASSKTTKDVVQTSAGSSEAKDSAPLQKANIKNTNDGHTQSQNNKN
SEQ5 (448) ----------
Becker (501) DNKQSPSVEKEIDASSESGKDKTPATKPAKGEVESSSTTPTKVVSATQNVAKPTSASSETTKGVVQTSAGSSEAKDMASLQKANIKNTNDGHTQSQNNKN
601 644
SEQ1 (447) ----------
SEQ3 (562) TQENKAKS----------
SEQ4 (563) TQENKAKS----------
SEQ5 (448) ----------
Becker (601) TQENKAKSLPQTGEESNKDMTLPLMALLALSSIIAFVLPRKRKN

RELATED PROCEEDINGS APPENDIX

None